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Increased symptoms of anxiety and depression in prepubertal girls, but not boys, with premature adrenarche: associations with serum DHEAS and daily salivary cortisol concentrations

Chrisanthi Marakaki^a, Panagiota Pervanidou^b, Ioannis Papassotiriou^c, George Mastorakos^d, Ze'ev Hochberg^e, George Chrousos^b and Anastasios Papadimitriou^a

^aThird Department of Pediatrics, Endocrinology Unit, School of Medicine, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece; ^bFirst Department of Pediatrics, Childhood Obesity Clinic, School of Medicine, Aghia Sophia Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece; ^cDepartment of Clinical Biochemistry, "Aghia Sophia" Children's Hospital, Athens, Greece; ^dSecond Department of Obstetrics and Gynecology, Endocrine Unit, Aretaieion Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; ^eFaculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT

Concerns over anxiety and depressive symptoms in children with premature adrenarche (PA) have been recently raised. However, to date, most relevant studies are on a small number of girls. In this cross-sectional study, 82 pre-pubertal children (66 girls and 16 boys) diagnosed with PA, were compared to 63 control children regarding their psychological characteristics and hypothalamic–pituitary–adrenal (HPA) axis function, as assessed by salivary cortisol measurement. Symptoms of anxiety and depression were assessed by child self-report (Spence Children's Anxiety Scale (SCAS) and Depression self-rating scale for Children (DSRS)) and parent-report (Child Behaviour Checklist (CBCL)) tests validated for the Greek population. Salivary cortisol levels were determined directly after awakening (approximately 7am) and evening (8pm) of the same day. Morning serum DHEAS levels were assessed in PA children. Girls with PA scored significantly higher on anxiety ($p=.016$) and depression ($p=.039$) scales than controls. No group differences were noted for parent reports and children's salivary cortisol concentrations. Boys with PA did not demonstrate significant differences in any of the aforementioned parameters. Our findings suggest that girls with PA may be at higher risk for reporting symptoms of anxiety and depression than their non-PA peers. HPA axis dysregulation in this population was not documented.

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Premature adrenarche; anxiety; depression; salivary cortisol; DHEAS; children

1. Introduction

Premature adrenarche (PA) is defined as the early appearance (before the age of 8 years in girls and 9 years in boys) of clinical signs of androgen activity (pubic and/or axillary hair, adult-type body odor, oily hair, and acne) and it may be accompanied by an increase in serum adrenal androgen levels, mainly DHEAS. The etiology of PA is multifactorial. Environmental factors (such as intrauterine growth restriction and obesity) and genetic factors (genes encoding steroidogenic enzymes, insulin-IGF signaling, and androgen receptor sensitivity) have been associated with PA. Pituitary ACTH is essential for adrenal androgen production, as evidenced by the absence of adrenarche in children with hypopituitarism and in patients with ACTH receptor defect (Voutilainen & Jaaskelainen, 2015). Exaggerated reactivity of HPA axis has been proposed to account in part for the development of adrenal hyperandrogenism in PA girls (Cizza et al., 2001). However, ACTH is not considered to be the trigger for adre-

narche and its initiating mechanisms remains at least partly obscure.

There are only a few studies on the psychological characteristics of children with PA. Most of them are underpowered (Cizza et al., 2001; Dorn, Hitt, & Rotenstein, 1999; Nass, Baker, Sadler, & Sidtis, 1990; Schoelwer et al., 2015), and the assessment was performed only in PA girls. Higher rates of psychosocial problems have been reported in 40 girls with PA than in their healthy peers (Dorn et al., 2008; Sontag-Padilla et al., 2012; Tissot et al., 2012), whereas other studies in girls with a history of PA or with PA did not find such an association (Nass et al., 1990; Schoelwer et al., 2015).

Given the discrepancy of the studies examining the psychology of girls with PA and the lack of relevant studies on PA boys, we aimed to examine the psychological profiles of girls and boys with PA at the time of diagnosis, through self- and parent-reported questionnaires. Furthermore, to examine for possible dysregulation of the HPA axis in PA children, we

assessed morning DHEAS blood levels and morning and evening salivary cortisol concentrations.

2. Subjects and methods

2.1 Subjects and protocol

A total of 145 pre-pubertal children of Greek origin, aged 5–11 (mean 7.77 ± 1.24 SD) years, were recruited from the pediatric endocrine clinic at “Attikon” University Hospital. They comprised 82 newly diagnosed children with PA (66 girls/16 boys), as previously described (Marakaki et al., 2017), and 63 (48 girls/15 boys) age-matched healthy children that served as controls. None of the children with PA had signs of virilization other than those associated with adrenarche, i.e. pubic and/or axillary hair, acne, apocrine odor, nor any chronic disease. Control children presented to our outpatient clinic mainly for thyroid evaluation (usually mild elevation of TSH levels) that, with the appropriate laboratory investigation, was shown to be normal. In each patient and control subject, height and weight were measured at presentation. Pubertal development was assessed clinically (physical examination by a physician) according to the Tanner criteria and only pre-pubertal children were included in the study, i.e. girls had absence of breast development and testicular volume of boys was <4 ml.

Blood samples for DHEAS were obtained between 7 and 9am, after an overnight fast in PA children. Salivary samples for cortisol were collected at home, on a typical school day in both PA and control children. Two samples were collected per day (approximately 7am directly after awakening and 8pm pre-bed) using a Salivette device (Sarstedt, Nuembrecht, Germany). Participants were not receiving any medications. Children were told not to eat, drink, brush their teeth, or exercise for at least 1 h prior to sample collection. Each of the samples was collected by having the participant place a cotton swab in his or her mouth for 2 min, or chews it for 1 min. The cotton was then placed inside a plastic tube and kept in the refrigerator at $0-4^{\circ}$ C.

The study was approved by the Ethics Committee of the “Attikon” University Hospital, and informed consent was obtained by the parents of the children participating in the study.

2.2 Psychometric instruments

All children completed the Spence Children’s Anxiety Scale (SCAS), a 45-item scale measuring symptoms of anxiety (Spence, 1998) and the Depression self-rating scale for Children (DSRS) an 18 item scale, which assesses depressive symptoms (Birlerson, Hudson, Buchanan, & Wolff 1987). Both tests have been validated in the Greek population (Giannopoulou, Dikaiakou, & Yule, 2006; Mellon & Moutavelis, 2007) and all items were coded such that a higher score indicated a higher level of anxiety and depressive symptoms, respectively, and the sum of items was used in the analysis. SCAS scale assesses six domains of anxiety including generalized anxiety, panic/agoraphobia, social phobia, separation anxiety, obsessive-compulsive disorder, and physical injury

fears. The alpha Cronbach for SCAS-GR (Greek version) is 0.86. The reported normal values for the SCAS scale are <50 for girls and <40 for boys (T-score <60). The DSRS is used to identify children with dysphoric mood in response to environmental stress and to measure change in emotional status. The children were asked to rate their own state during the last week on a 3-point Likert scale (0 = Never, 1 = Sometimes, and 2 = Most of the time), with eight items being scored in reversed order. The total score, which was one of the outcome measures, has demonstrated adequate internal consistency (Cronbach $\alpha=0.81$). A suggested score of 15 and over has been validated in a Greek clinical sample (Giannopoulou et al., 2006), as an efficient cutoff for identifying youngsters at risk for clinical depression.

All parents completed the Child Behaviour Checklist (CBCL) for ages 6–12 years (Roussos et al., 1999; Achenbach & Rescorla, 2001). The Greek Version of the CBCL was used to assess internalizing and externalizing symptoms in children. As conceived by Achenbach in 1991, internalizing symptoms refer to problems of withdrawal, somatic complaints, and anxiety/depression, while externalizing symptoms are presented in delinquent and aggressive behavior. The CBCL consists of 113 items using a 3-point scale. The alpha Cronbach for internalizing and externalizing problems in the Greek version of CBCL is 0.90 and 0.94, respectively. The data obtained by these questionnaires were inserted into the Achenbach System of Empirically Based Assessment (ASEBA) computerized system and T-scores and percentiles of symptoms, based on Greek Norms, were calculated.

The questionnaires were filled at the time of the initial visit to the clinic, in the majority of the children included in the study, after the first clinical examination of the child and before any blood sampling in the PA children. The families of the PA children were not fully informed at that time about the condition, as laboratory investigation was pending, but were reassured about its benign course. The families of the control children were asked to participate in the study following normal results of the appropriate laboratory investigation, usually about mild TSH elevation.

2.3 Hormone measurements

DHEAS was measured by solid phase, competitive, chemiluminescent immunoassay (Diagnostic Products Corporation, Los Angeles, CA) with a sensitivity of 30 ng/ml, intra-assay coefficient variation 6.8–9.5%, inter-assay coefficient variation 8.1–15 and 8–15% of total variability. The salivary samples were given to the investigator within 3 d after collection for further processing. Salivary cortisol was extracted from the cotton by centrifuging the plastic tubes and cotton at 1000 g for 8 min to separate off the saliva into the outer tube. The cotton was then removed and all samples were stored at -85° C. Samples were processed using the Elecsys Cortisol II reagent kit produced by Roche Diagnostics, Risch-Rotkreuz Switzerland. Salivary cortisol levels were determined using an electrochemiluminescence immunoassay (Roche Cobas E411). The analytical sensitivity for salivary cortisol was <1.5 nmol/l.

Table 1. Characteristics of the children with premature adrenarche and controls.

	Premature adrenarche <i>n</i> = 82		Controls <i>n</i> = 63		<i>p</i> Values*	
	Girls <i>n</i> = 66	Boys <i>n</i> = 16	Girls <i>n</i> = 48	Boys <i>n</i> = 15	Girls	Boys
Age (year) at presentation	7.39 (0.95)	8.95 (1.10)	7.65 (1.30)	8.53 (1.26)	.246	.339
Age (year) at adrenarche	6.36 (1.10)	7.76 (0.63)	–	–	–	–
HSDS at presentation	0.68 (0.98)	1.11 (0.98)	0.17 (1.16)	0.037 (1.10)	.015	.008
BMISDS at presentation	1.28 (1.16)	2.09 (0.74)	0.85 (1.04)	0.89 (1.32)	.041	.006

Results are presented as mean (SD).

*Independent samples Student *t*-test.

HSDS: height standard deviation score.

Table 2. Self-reported psychological assessments in premature adrenarche and control children.

Tests	Premature adrenarche		Controls		<i>p</i> Values*	
	Girls <i>n</i> = 66	Boys <i>n</i> = 16	Girls <i>n</i> = 48	Boys <i>n</i> = 15	Girls	Boys
SCAS T-scores	45.03 (7.98)	45.00 (10.53)	41.31(8.09)	44.60 (9.83)	.016	.914
DSRS scores	7.50 (3.0)	7.38 (3.9)	6.29 (3.1)	5.60 (3.1)	.039	.177

Results are presented as mean (SD).

*Independent samples Student *t*-test.

SCAS: Spence Children's Anxiety Scale; DSRS: depression self-rating scale for children.

Table 3. Salivary cortisol levels (nmol/l) in premature adrenarche and control children.

	Premature adrenarche <i>n</i> = 58		Controls <i>n</i> = 32		<i>p</i> Values*	
	Girls <i>n</i> = 50	Boys <i>n</i> = 8	Girls <i>n</i> = 26	Boys <i>n</i> = 6	Girls	Boys
morning	11.33(5.82)	9.79(3.09)	10.45(5.49)	16.42(10.68)	.527	.194
evening	<1.5	<1.5	<1.5	<1.5	–	–

Results are presented as mean (SD).

*Independent samples Student *t*-test.

2.4 Statistical analyses

Statistical analyses were performed with the use of SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL). Continuous data are presented as mean \pm SD. Kolmogorov–Smirnov test was used to assess normality for the distribution of continuous variables. Group differences were examined using Student *t*-test for the following continuous measures: presentation age, BMISDS, height standard deviation score (HSDS), self and parent report test scores, and salivary cortisol concentrations. Pearson's correlation coefficient was used to assess the linear association between quantitative variables (self and parent report test scores with HSDS and BMISDS, Tanner stages, DHEAS levels of the PA children). The groups were also compared by ANCOVA, using as covariates BMISDS, HSDS, and morning salivary cortisol levels. Statistical significance was defined as a two-sided $p < .05$.

3. Results

Anthropometric characteristics of the PA and control children are shown in Table 1. Mean (SD) age at presentation for girls and boys with PA was 7.39 (0.95) and 8.95 (1.10) years, respectively. Age of control children was 7.65 (1.30) for girls and 8.53 (1.26) for boys (NS). Girls and boys with PA were taller and had more adipose than controls. Reported age at adrenarche was 6.36 (1.10) years for girls and 7.76 (0.63) years for boys. Additional data on auxological and biochemical characteristics were published recently (Marakaki et al., 2017).

3.1 Psychological assessment

Results on self reported tests of psychological assessment are outlined in Table 2. Self reported questionnaires (SCAS and DSRS) revealed a significant increase in anxiety ($p = .016$) and depressive symptomatology scores ($p = .039$) in girls with PA in comparison to controls, while no difference was identified in boys. In 3/66 (4.5%) of the girls with PA vs. 1/48 (2.1%) of the controls and in 3/66 of girls with PA (4.5%) vs. 2/48 (4.1%) of controls scores were elevated above what would be regarded as normal levels within the community for anxiety and depression, respectively. By parent report on the CBCL, no significant differences were found between the two groups (data not shown).

3.2 Salivary cortisol and DHEAS levels assessment

Morning salivary cortisol concentrations were measured in 58 children with PA and 32 controls and found to be within normal levels and comparable (Table 3). Evening salivary cortisol levels were below the detection limit of the method (<1.5 nmol/l) in children with PA and controls. Basal serum DHEAS levels were slightly elevated for chronological age, i.e. mean DHEAS 101.8 (52.8) ng/dl for girls and 152.5 (77.2) ng/dl for boys (normal range: 9–72 ng/dl). No significant correlation was found between anxiety and depressive scores with the anthropometric characteristics (HSDS and BMISDS), Tanner stages or DHEAS levels of the children with PA. The groups were also compared by ANCOVA and the results remained positive even after adjusting for BMISDS, HSDS and salivary cortisol.

4. Discussion

In this study, we showed an increased prevalence of anxiety and depressive symptoms in girls, but not in boys, with PA, as documented through population standardized self-reported measures. The mean scores of girls with PA, in all self-reported scales, were within normal range, but significantly higher than in the non-PA girls. Parental reports failed to detect any differences between girls with PA and controls, but this can be attributed to the fact that the children's self reported scores fell into the normal range and that the children did not exhibit clinical symptoms. Self reported anxiety and depressive symptoms are considered more accurate than parental reports, because children tend to internalize their problems and do not communicate easily their anxiety to their environment (La Greca, 1990).

Our findings are in line with earlier studies documenting internalizing symptoms in girls with PA, i.e. behaviors that result from negativity that is focused inward such as social withdrawal, fearfulness and low self-esteem (Dorn et al., 1999; Dorn et al., 2008; Sontag-Padilla et al., 2012; Tissot et al., 2012). These reports were from the same research group, which studied extensively 40 girls with PA and found significantly more anxiety, as well as oppositional defiant and mood disorder symptoms, as reported from parents and teachers. However, no group difference in child-reported depressive and anxious symptoms was observed. The first study (Dorn et al., 1999) reported higher concentrations of serum and saliva cortisol in 9 children with PA compared to 20 on-time adrenarche children. In a subsequent study, cortisol reactivity was assessed using venipuncture as a stressor; no differences in blood cortisol levels (3 samples) between 40 PA and 36 on-time adrenarche girls were noted (Dorn et al., 2008). In a recent study (Schoelwer et al., 2015) on the psychological profile of mothers of 22 girls with PA, the authors reported more symptoms of stress and depression, suggesting that such symptoms in parents of children with PA may also influence the accuracy of the reported psychological symptoms in their affected children. Another option is that stress and depression in mothers may cause PA in their children. In the same study, psychological adjustment scores of girls with PA were normal, however, only 4 girls with PA were evaluated for depressive symptoms.

Differences in anthropometric characteristics of children with PA (higher BMISDS and HSDS) compared to their peers could provoke emotional and behavioral disorders, and lower self-esteem in children with PA due to stigma, teasing, and/or bullying. There is evidence that pediatric obesity commonly co-exists with anxiety and depression and influences health-related quality of life (Pervanidou et al., 2015; Williams, Wake, Hesketh, Maher, & Waters, 2005). In our study, no correlation was established between anthropometric characteristics of the children with PA and their self-reported psychological scores and salivary cortisol concentrations. Thus, greater anxiety and depressive symptoms reported in this study; could not be attributed to the physical changes of PA. The first clinical signs of androgen action (pubic and axillary hair, adult-type body odor, oily hair, and acne) may cause some discomfort to the young girl, but we assumed that they did not significantly contribute to the psychological symptoms reported because they were quite subtle at the time of diagnosis. Moreover, in our study, psychological assessment of the children with PA was performed at the time of initial presentation to the clinic, thus repeated medical evaluation was excluded as a stressor.

The possibility that girls with PA are more self-aware and self-reflective, or are more willing to report their feelings, and are not necessarily more anxious or depressed than their peers should be taken into consideration. Campbell suggested that DHEAS may promote changes in behavior and cognition (Campbell, 2006), through acting on the amygdala to reduce fearfulness and allow for the expression of an increased range of social interactions with unfamiliar individuals, as the juvenile cares for his new needs and interacts with peers.

Girls with PA may present polycystic ovarian syndrome later in their reproductive age. Recent guidelines suggest that women and adolescents with PCOS be screened for anxiety and depression (Legro et al., 2013). The increased prevalence of depression and depressive symptoms in women with PCOS appears to be independent of obesity, androgen levels, hirsutism, acne, and infertility, which is in accordance with our results in PA girls.

Our findings of normal cortisol salivary concentrations and the lack of correlation between anxiety or depressive symptoms and DHEAS levels in PA children suggest that subclinical symptoms of anxiety and depression do not seem to be overtly related to HPA axis activity. However, a recent study in 9.5-year-old children of both sexes (Murray et al., 2016) suggests an indirect link between relatively high DHEAS/DHEA levels and symptoms of social anxiety, mediated by increased pituitary gland volume and that DHEAS/DHEA levels independently did not affect anxiety symptoms. Thus, it seems that neurobiological mechanisms are partly responsible for the link between PA and anxiety symptoms in children.

Limitations of the study are the cross-sectional nature of its design, which limits the generalizability of our findings, the small number of PA boys, which is justified by the reported low prevalence of PA in boys (Voutilainen & Jaaskelainen, 2015), and that control children were not recruited from the community, although these children were examined and investigated by us assuring they were healthy. Moreover, the non-statistical difference in anxiety and depression tests scores in boys may be due to their small number. Measurement of the diurnal rhythm of cortisol secretion using a greater number of serial salivary samples might provide more information on HPA axis status in children with PA.

5. Conclusion

Our study suggests that girls with PA are at higher risk for reporting symptoms of anxiety and depression than their non-PA peers, irrespectively of their BMI at diagnosis. The mechanism is unclear, and we could not document hyperactivity of the HPA axis. Health care providers that follow children with PA should be aware of the possibility that girls may develop emotional and behavioral problems. Early identification of these problems is of great importance for optimizing their management, especially in view of the imminent pubertal onset.

Disclosure statement

The authors have no financial relationships or conflicts of interest to disclose relevant to this article.

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